Cloning of the human cDNA for transcription factor Pit-1

April M.Lew and Harry P.Elsholtz*
Department of Clinical Biochemistry and the Banting and Best Diabetes Centre, University of Toronto, 100 College Street, Toronto, Ontario M5G 1L5, Canada

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The mammalian *pit-1* gene encodes a 33 kd transcription factor (1, 2) expressed in a subset of endocrine cells of the anterior pituitary (3). Pit-1 is structurally related to the POU family of transcriptional regulators (4), containing a characteristic POU domain divided into two regions, the POU-specific and homeo subdomains. Located in the C-terminal half of the protein, the POU domain is critical for high affinity binding of Pit-1 to specific AT-rich sequences in target genes (eg. prolactin, growth hormone) and appears necessary for the DNA-dependent dimerization of the factor (5). N-terminal residues of Pit-1 provide the major transactivation domain (5, 6).

The importance of Pit-1 as a regulator of anterior pituitary development has been demonstrated in studies of dwarf mouse strains that have hypoplastic anterior pituitares and a conspicuous absence of three pituitary cell types — lactotrophs, somatotrophs, and thyrotrophs. Immunostaining with Pit-1 antibodies showed that levels of Pit-1 expression in these mice is low or undetectable (7). In one of the strains (Jackson dwarf) a gross rearrangement of the *pit-1* gene was revealed by RFLP analysis, whereas in a second (Snell dwarf) a point mutation in the homeodomain results in a Trp→Cys alteration that abolishes DNA-binding activity of the mutant protein (7). Loss-of-function mutations in the *pit-1* gene demonstrate that Pit-1 may be critical to the proliferation or survival of specific cell lineages of the anterior pituitary. A recent report in which oligonucleotides complementary to Pit-1 mRNA inhibit ^{3}H-thymidine incorporation by somatotroph and lactotroph cell lines further implicates Pit-1 in the cell-specific regulation of DNA replication (8).

In humans, the role of Pit-1 in normal development or abnormal proliferation of specific pituitary cell types has not been determined. We report here the complete nucleotide and deduced amino acid sequence of the human Pit-1 cDNA isolated from a pituitary tumor library (λgt10, Clontech). Screening of the library was performed at high stringency using a probe (corresponding to Pit-1 amino acid residues 142 to 264, see ref. 1) synthesized from human somatomammotroph adenoma cDNA by PCR. Positive clones were sequenced by the dideoxy method (Sequenase, USB). The open reading frame of the human Pit-1 cDNA predicts a 291 amino acid protein that is 96% identical to other mammalian Pit-1s. Table 1 shows that the majority of amino acid substitutions are found in the N-terminal half of human Pit-1 (93% identity), whereas the 142 residue Pit-1 POU domain is 97 to >99% identical among mammalian species.

The highly conserved structure of human Pit-1 is consistent with a common developmental role for this factor in rodents and primates. Developmental defects in humans caused by an under-expressed or non-functional *pit-1* gene would appear to be rare, however, since most patients with dwarfism have a normal somatotroph morphology. An interesting case suggestive of decreased Pit-1 expression or function has recently been presented by Asa and colleagues (9). Two siblings with dwarfism and hypothyroidism were noted at autopsy to have pronounced hypoplastic anterior pituitaries. Immunoreactivity of adrenocorticotrophin, luteinizing hormone and follicle-stimulating hormone was normal in both cases, whereas prolactin, growth hormone and thyroid-stimulating hormone were undetectable. Genomic DNA analysis may reveal whether mutations or rearrangements in the *pit-1* gene could explain the developmental defect in this and related familial disorders.

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Table. Distribution of amino acid substitutions in human Pit-1. Coordinates for residues are those used in ref. 4. Abbreviations are h, human; r, rat; m, murine; b, bovine.

				POU Subdomains				
	Total 1–291	N-term. 1–129	POU domain 130–271	$POUS_s$-A 132–160	POU_s-B 166–198	Homeo 213–271	'WFC' 255–271	C-term. 272–291
h:r	12/291	9/129	3/142	1/29	0/33	2/59	0/17	0/20
h:m	13/291	9/129	4/142	1/29	0/33	3/59	0/17	0/20
h:b	11/291	9/129	1/142	0/29	0/33	1/59	0/17	1/20

* To whom correspondence should be addressed